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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/976,560	11/24/97	FREIMER N	UCAL-250-02U

HM12/0728

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EXAMINER	
ARTHUR, L	
ART UNIT	**PAPER NUMBER**
1655	7

DATE MAILED: 07/28/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/976,560	Applicant(s) Freimer et al.
	Examiner Lisa Athur	Group Art Unit 1655

☒ Responsive to communication(s) filed on *May 3, 1999*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-16* is/are pending in the application.

Of the above, claim(s) *14* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-13, 15, and 16* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *6*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. This action is in response to the paper filed May 3, 1999 in which applicant elected Group I, claims 1-13, 15 and 16. Claims 14 has been withdrawn from the examination.

2. Applicant's election of Group I in Paper No. 5 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. Figure 2 is objected to because the figure is described as "Table 1" which is in conflict with its designation as Figure 2.

4. Claim 5 is object to over the recitation of "at201" because the specification and the other claims refer to this marker as "ta201".

5. Claims 5 and 6 are objected to because they appear to be duplicative claims.\

6. Claim 16 is objected because it does not further limit claim 15.

7. Claims 2-7, 9-13, 15 and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2-7,9-13, 15 and 16 are indefinite over the recitation of "inclusive" because as written the claims are unclear as to what "inclusive" is referring to. If the term is intended to mean that the method includes detecting polymorphisms between and inclusive of the recited markers, then the rejection can be overcome by amending the claims to instead recite "between and inclusive of SAVA5 and ...", for example.

8. Claims 1-13, 15 and 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of detecting an increased susceptibility for bipolar mood disorder by performing a pedigree analysis for the individual's family and analyzing the DNA from all family members for linkage of markers on the short arm of chromosome 18 between and inclusive of SAVA5 and ga203, D18S1140 and ga203, SAVA5 and W3422, S18S1140 and W3422, D18S1140 and ta201 and S18S59 and ta201 , does not reasonably provide enablement for a method of detecting a locus for bipolar mood disorder by detecting polymorphisms between and inclusive of SAVA5 and ga203 or any of the other recited markers. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims, as written, are not commensurate in scope with the disclosure in the specification because the specification has not provided sufficient guidance in light of the teachings in the art to enable the skilled artisan to detect a bipolar mood disorder susceptibility locus without undue experimentation for the reasons which follow. The art teaches that a while linkage has been shown between several different chromosomal regions and bipolar mood disorder, susceptibility locus for this disease has yet to be identified. Stine et al. (AM J. HUM GENET. (1995) 57:1384-1394) showed evidence of linkage between bipolar disorder and markers on the short art of chromosome 18, i.e. 18p including marker D18S59 (table 1) and showed a parent-of-origin effect operating in this disease, but acknowledged that the number of

loci and their precise location require further study (page 1392, col. 2). McInnes et al. (PNAS (1996) 93:13060-13065) teach that interpreting results from linkage analysis of bipolar mood disorder and other behavioral phenotypes is very difficult and often misleading because behavioral phenotypes are difficult to define, are etiologically heterogenous and there is a lack of knowledge as to the mode of transmission of these diseases. McInnes et al concluded that it is unlikely that any one linkage study will yield sufficient evidence to localize a gene for any psychiatric disorder (page 13060, col.2, paragraph 1). However, McInnes et al. Performed a genome screening analysis for possible genes associated with bipolar disorder and found suggestive lod scores in segments of 18q 18p and 11p (see abstract and Table 1) including marker D18S59. McInnes et al. states that the point of their study was to detect regions which merited further investigation (page 13063, col. 1, para. 1) and specifically identified the telomere of 18p as a region to further study (page 13064, col. 1, para 1). McInnes et al. States that genome screening is a first stage of a multi step process for identifying genes for complex traits (page 13064, col. 2, para. 2). McInnes et al. Taught that the second and third stages int he precess were delineating clear candidate regions and fine mapping studies. Esterling et al. (MOLECULAR PSYCHIATRY (1997) 2:501-504) constructed a high resolution integrated map pf 18p11.2 which is a 40cM region which they state contains a potential bipolar susceptibility locus (see Figure 1). However, even with these high resolution maps and linkage studies even as 1999 no specific polymorphisms or loci have been identified as a bipolar susceptibility locus. Ewald et al. (Psychiatric Genetics (1997) 7:1-12) teach that while chromosome 18 is one of the most promising chromosomes to

contain a bipolar susceptibility locus, the research is still considered a search for susceptibility genes (see abstract). Gerson et al. (Neuropsychopharmacology (1998) 18(4): 233-242) reviewed the progress in identifying genes for manic-depressive illness and concluded that while chromosome 18 including the short arm of chromosome 18 is one of the best candidate locations for a bipolar susceptibility, and that the positive linkage results represent important progress, scientists are yet a long way from demonstrating disease mutations in bipolar illness (page 239, col. 2, para. 2, bottom). Nothen et al. (Molecular Psychiatry (1999) 4(1): 76-84) concluded as late as 1999 that the data in the art supports the hypothesis that a susceptibility locus exists and may exist on chromosome 18, but does not provide a reasonable expectation as of yet that polymorphisms in the region of 18p is associated with a bipolar susceptibility locus or what that locus will be.

The specification teaches that the marker D18S59 showed the strongest evidence for linkage to bipolar disease (page 24-25) The specification then teaches that cloned human DNA from this region, i.e. a 5cM region of chromosome 18 "is" assembled (page 25) . Markers within a 500kb and 300 kb subregion were used to delineate regions of bipolar susceptibility with the 5 cM 18pter region and blood from 105 affected individuals were tested for marker haplotypes. Figure 7 shows 18p allele frequencies and showed evidence of particular alleles being over represented on disease chromosomes. The comparisons in the figures was found to show that the region of maximal sharing between affected individuals occur between 1140t and w3442 on chromosome 18 which is a region of about 300 kb. The specification then teaches that the

sequences within these regions is then analyzed for expressed sequences and sequences which are associated with bipolar disorder.

The teachings in the specification do not provide the skilled artisan with a reasonable expectation that he will identify polymorphisms that are associated with bipolar mood disorder or for detecting a bipolar susceptibility locus without undue experimentation because of the extensive amount of unpredictability in this field as shown by the above analysis of the prior art and because the specification has not provided evidence that would allow the skilled artisan to predict that where and what the bipolar susceptibility locus will be. The specification appears to present data defining a smaller region of the 18pter which has a higher probability of possibility containing a susceptibility locus but the art as of 1999 still states that scientist are a long way from pinpointing a locus or polymorphisms which are predictability associated with bipolar disease. Furthermore, the claims as written are claims to a research project without a predictable outcome but which encompass the detection of a bipolar disease gene. The art makes clear that this objective is of great interest and the target of extensive research by many groups. In fact many groups are taking the same approach as described in the specification for identifying such a bipolar locus without success. The fact that the specification presents evidence of linkage to the recited markers to a smaller region than is taught by the art would provide information within families of affected individuals such that an increased risk of developing bipolar mood disorder could be predicted in a particular family member by doing a pedigree analysis using the markers disclosed int he specification and recited in the claims showing maximal sharing between affected

individuals. The specification however does enable the skilled artisan to detect a bipolar mood disorder locus by detecting polymorphisms within the recited region without undue experimentation for the reasons given above.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 15 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Stine et al. (AM J. HUM. GENET. 57:1384-1394(1995)).

STINE et al. Teach an isolated polynucleotide which is marker D18S59 which they showed was linked to bipolar mood disorder. Therefore, Stine et al. Teach the claimed isolated polynucleotide because the specification taught that this marker is located within the 500kb region between SAVA5 and ga203 even though Stine et al. Did not define the 500kb region disclosed in the specification.

11. No claims are allowable. However, it is noted that the prior art did not define a 500 kb region of 18pter between SAVA5 AND ga203 as being linked to bipolar disorder.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa Arthur whose telephone number is (703) 308-3988. The examiner can normally be reached on Monday-Wednesday from 7:00AM to 2:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Lisa B. Arthur

LISA B. ARTHUR
PRIMARY EXAMINER
GROUP ~~1800~~ 1600

July 19, 1999